

### Influenza—Promising New Developments

DR. CHARLES H. STUART-HARRIS in a recent address concluded a tribute to Sir Christopher Andrewes (co-discoverer of the influenza virus) and to Dr. Thomas Francis Jr. (discoverer of influenza B and director of the first influenza vaccine trial) with the following statement: "Thirty-seven years after the discovery of the virus and in spite of all the wealth of knowledge which we possess, it remains a fact that we are still defeated by its prowess." The tragic case of fatal influenza in pregnancy which served as a basis for the UCLA Staff Conference which appears elsewhere in this issue is adequate testimony to the validity of this statement. Nevertheless, progress has been made toward effective control of influenza, and there is reason to be optimistic about the future. A consideration of some current lines of investigation that relate to control is in order.

The most recent contribution to a fundamental understanding of resistance to influenza has been provided by studies on the neuraminidase antigen. There are two major antigens on the surface of influenza virions, the hemagglutinin and neuraminidase. The hemagglutinin spike is known to be the site of attachment to the cell surface for initiation of infection, and neuraminidase has recently been shown to facilitate release of new virus particles from the surface of infected cells. Resistance to infection correlates with the presence and magnitude of the titer of antibody to the hemagglutinin antigen. In contrast, antibody to neuraminidase does not prevent infection but appears to limit the spread within an infected animal as well as spread to other animals. Thus, infected animals with neuraminidase antibody and no hemagglutinin antibody have lower lung virus titers, less pneumonia, and less ability to transmit influenza than animals with neither type of antibody. Knowledge of the epidemiologic factors and clinical manifestations of infection with the Hong Kong variant suggests that similar phenomena occur in man.

In studies of antigenic relatedness between the two major surface antigens, it was found that the Hong Kong variant possesses a unique and new hemagglutinin antigen but that the neuraminidase antigen is similar to that of 1967 strains of type A influenza. This is in contrast to the Asian strain introduced in 1957 in which both antigens were decidedly different from those present in earlier strains (subtype A<sub>1</sub>). In fact, the hemagglutinin

antigen of the Hong Kong variant is so markedly different from 1957 strains it has been suggested that either the Hong Kong variant should have been called A<sub>3</sub> or we should revise criteria for classification. Assuming the animal data on the role of neuraminidase antibody applies to man and that neuraminidase antibody persists for one to two years (questions that are being investigated) then a reasonable prediction for the 1968-69 influenza season would have been that influenza would not achieve a worldwide pandemic state similar to that seen in 1957 and that pure influenza virus pneumonia, as distinguished from secondary bacterial pneumonia, would not be as common as in 1957. It is now a fact that the Hong Kong variant did not achieve the pandemic proportions of 1957. In addition, although the infection reached major epidemic proportions in the United States, surveys of medical centers indicated that cases of pure influenza virus pneumonia were uncommon.

It is essential to confirm the suggested role for neuraminidase antibody in man, and such studies are in progress in our laboratory and in others. Immunization of school children, the principal source of spread, with a purified form of the neuraminidase and hemagglutinin antigens, and immunization of all other persons with neuraminidase antigen only, might prevent epidemic influenza by reducing spread of infection. Additionally, widespread occurrence of hemagglutinin antibody, the presumed major stimulus for emergence of new variants, would not occur in this method of control.

Production of antibody to the hemagglutinin antigen of influenza virus by means of conventional vaccination continues to be the major approach to control. Development of serum antibody following parenteral vaccination with inactivated virus has been used for assessing vaccine efficacy since Francis conducted the first successful field trial in 1943. In the early 1940s Francis reasoned that the virus initially was deposited on the respiratory mucosa and that, to prevent initiation of infection, antibody must be present in respiratory secretions. He proceeded to demonstrate that antibody was present in secretions but believed it was derived from serum and that parenteral vaccination did an adequate job of providing secretion antibody. Studies by Fazekas de St. Groth in the early 1950s provided definitive information in animals that protection against influenza was better associated with antibody in respiratory secretions than in serum, but he too believed it was derived from serum.

Current knowledge indicates that a separate immune system is involved in production of secretion antibody. The major portion of such antibody is immunoglobulin A which sediments in the 11S region in the ultracentrifuge. It consists of two 7S IgA molecules connected by "secretory piece" and is commonly referred to as secretory antibody. It is synthesized in the submucosa plasma cells of the respiratory and gastrointestinal tract and perhaps other mucous surfaces as well. In an attempt to use this system to maximum advantage investigators have administered conventional inactivated vaccine topically\* in an attempt to provide more local antibody and greater protection. The most systematic evaluation of the antibody response has been provided by Kasel, who demonstrated that topical administration of vaccine was the only effective way to achieve high titers of secretory antibody in individuals with preexisting serum antibody. This probably accounts for the greater protective effect reported for aerosol vaccination as compared with parenteral vaccination in studies with strains prevalent before 1968. However, conventional parenteral vaccination produced equal or better antibody responses and protection than topical vaccination in all reported studies with the Hong Kong variant. This is probably because one or two topical applications is inadequate for persons with no previous exposure to the antigen. These combined results suggest that primary vaccination with a new variant of influenza should continue to be by conventional parenteral vaccination. Antigen administered in this way apparently reaches submucosal cells since a potent preparation administered in such a way will result in development of secretory antibody in a significant number of persons. However, the best method to revaccinate may be by means of a topical route.

The two major reasons why influenza vaccines did not receive wide acceptance in the past even in "high risk" groups were that available preparations were only marginally effective and they were too toxic. The introduction of more rigid controls of potency using standard reference vaccines is now in effect. A precisely measured 400 CCA unit dose has been shown to produce protection of 70 to 80 percent of subjects when given by conventional parenteral vaccination. Thus, marginally effective preparations should no longer appear for distribu-

\*Topically is used to refer to application of vaccine onto respiratory surfaces by means of nasal instillations and/or inhalation of aerosolized vaccine.

tion. In addition, new preparations are being made by methods that remove potentially toxic chick embryo proteins. Such preparations of influenza A are virtually nontoxic. However, despite new preparation methods influenza B vaccine has caused toxic reactions and the frequency of antibody response is low. Currently, only preparations containing both influenza A and B are available, but it seems reasonable to suggest that the monovalent influenza A preparations are so potent and nontoxic that they should be commercially available as such and that influenza B be withheld until a potent, nontoxic preparation is available.

An additional problem regarding vaccination has been availability of sufficient vaccine to induce protection in a susceptible population before a new variant arrives on the scene. The worldwide influenza surveillance centers are for this purpose and the Hong Kong center was the original source of the Hong Kong variant. Despite the fact that the elapsed time from original isolations of the Hong Kong variant to distribution of vaccine was considerably reduced as compared with what it was in 1957 for the original Asian variant, very little vaccine reached threatened areas in this country before influenza appeared.

Kilbourne recently prepared a recombinant (by a method called "strand exchange" in this symposium) of the Hong Kong variant and the laboratory-adapted PR 8 strain of influenza. This recombinant (called x-31) carries the hemagglutinin antigen of the Hong Kong variant and the growth advantage of PR 8. This latter strain grows to high titers in chick embryos, thus facilitating vaccine preparation. We found vaccine made from this recombinant to be equal to conventional monovalent inactivated influenza A<sub>2</sub>/Hong Kong in producing antibody and protection in man. Similar preparation of a recombinant, then, should facilitate the rapid preparation of large quantities of vaccine when influenza A<sub>3</sub> makes its appearance, an event that is certain to occur.

Comment should also be made concerning chemotherapy of influenza. Amantadine (Symmetrel®) has been clearly shown to prevent infection with influenza A. It prevents penetration of the cell by virus, a mechanism similar to that of antibody. I believe it should be recommended for unvaccinated "high risk" persons when exposed to influenza, and a recent report suggested optimal protection would occur in such persons

if they possessed some preexisting antibody to influenza virus. It may be that vaccine in the fall followed by amantadine on exposure to influenza in the winter will produce optimal protection. The possibility warrants trial.

Recently we tested the drug as a therapeutic agent. In a recent Hong Kong influenza epidemic, our results indicated increased rate of recovery from illness and a more rapid disappearance of virus from respiratory secretions in treated versus control patients. The effect was not dramatic but was nevertheless significant. The dose used was that recommended for prophylaxis, namely, 200 mg daily. No toxicity was observed with this dosage, and it was therefore felt that for treatment one could give a larger dose. Recently we gave 400 mg daily to three patients who were ill with pneumonia complicating influenza, and one of them, a pregnant woman, recovered in dramatic fashion. Controlled studies of the treatment of influenza pneumonia are not likely to be possible, and we may be required to pass judgment on the effect of amantadine on rather inadequate information. On the basis of our experience, we believe further such studies are indicated.

All in all, there is reason to be encouraged about the future. As stated by Dr. Stuart-Harris, despite a wealth of knowledge we are still defeated by the prowess of influenza virus. The occasion of this symposium is testimony to that fact. Nevertheless, a considerable effort is being made to defeat this redoubtable foe. In addition to the promising new developments cited in this editorial, there are many theoretical possibilities for improved control not yet examined. Among epidemiologists it is considered to be hazardous but essential to predict how serious the problem of influenza will be in any given year. To predict whether or not in the next few years optimal control of influenza will occur is certainly hazardous. Nevertheless, I shall predict that optimal control measures will be developed which will result in reduction of influenza to acceptable levels of occurrence, and that this will occur in considerably less time than has elapsed since the discovery of its cause.

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#### REFERENCE

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